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(54) Process for the preparation of 4-substituted-1,4-dihydropyridines

Verfahren zur Herstellung von an 4-Position substituierten 1,4-Dihydropyridinen

Procédé pour la préparation des 1,4-dihydro-pyridines 4-substituées

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(56) References cited:
EP-A- 0 212 107
EP-A- 0 234 776
EP-A- 0 371 492
EP-A- 0 445 987
EP-A- 0 451 654

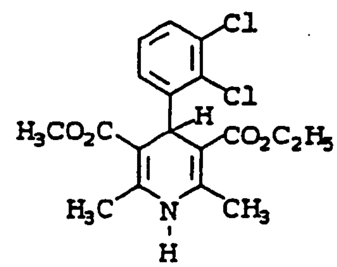
- Industrial & Engineering Chemistry, Product Research and Development (1982) 21(2), pp 139-261

EP 0 534 520 B1

Description

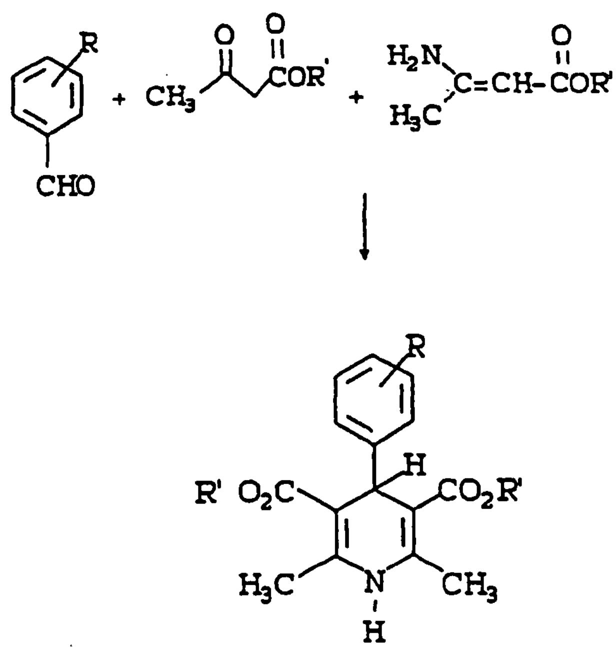
BACKGROUND OF THE INVENTION

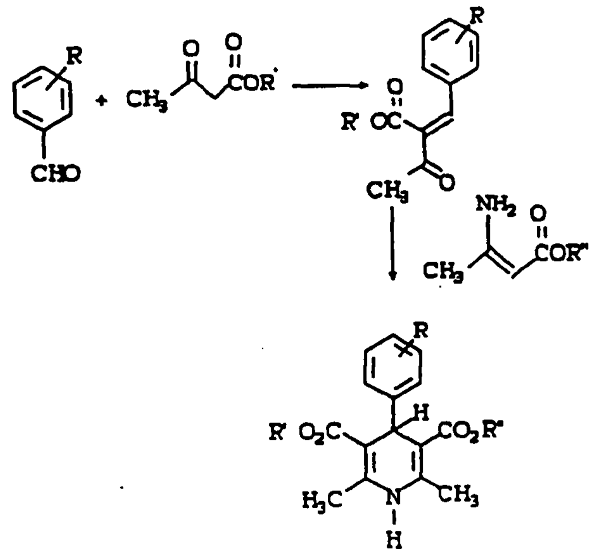
Felodipine, the compound of Formula Ib, is a known vasodilator (Merck Index 11,3895 and references cited therein). Other phenyl-1,4-dihydro- pyridine compounds have also been disclosed which have therapeutic activity in the treatment of heart disease (see for example: U.S. Pat. Nos. 4,220,649; 4,705,797; 4,769,374; 4,806,544; 4,874,773; and EPO Appl. Nos. 0 089 167, 0 063 365 and 0 342 182).



Ib

The preparation of felodipine and related compounds typically involves a multistep synthesis, the last step of which usually involves formation of the dihydropyridine ring. Formation of the 4-aryl dihydropyridines has been accomplished by either simultaneous reaction of an aromatic aldehyde, an acetoacetate ester and a 3-aminocrotonic acid ester in an alcohol solvent (see for example U.S. Pat. No. 4,264,611) or a stepwise procedure of reacting an aromatic aldehyde with an acetoacetate ester and then reacting the resulting benzylidene with a 3-amino crotonic acid ester (see for example: EPO Appl. No. 0 319 814). Regardless of whether the sequence of reactions is a single step or two steps, the disclosed cycloadditions have always been thermally driven to completion. Thermal cycloaddition reactions have also been described which are carried out in the presence of an organic base or the acetic acid salt of an organic base (see for example U.S. Pat. No. 4,772,596 and EP-O 370 974). The two procedures are illustrated below.

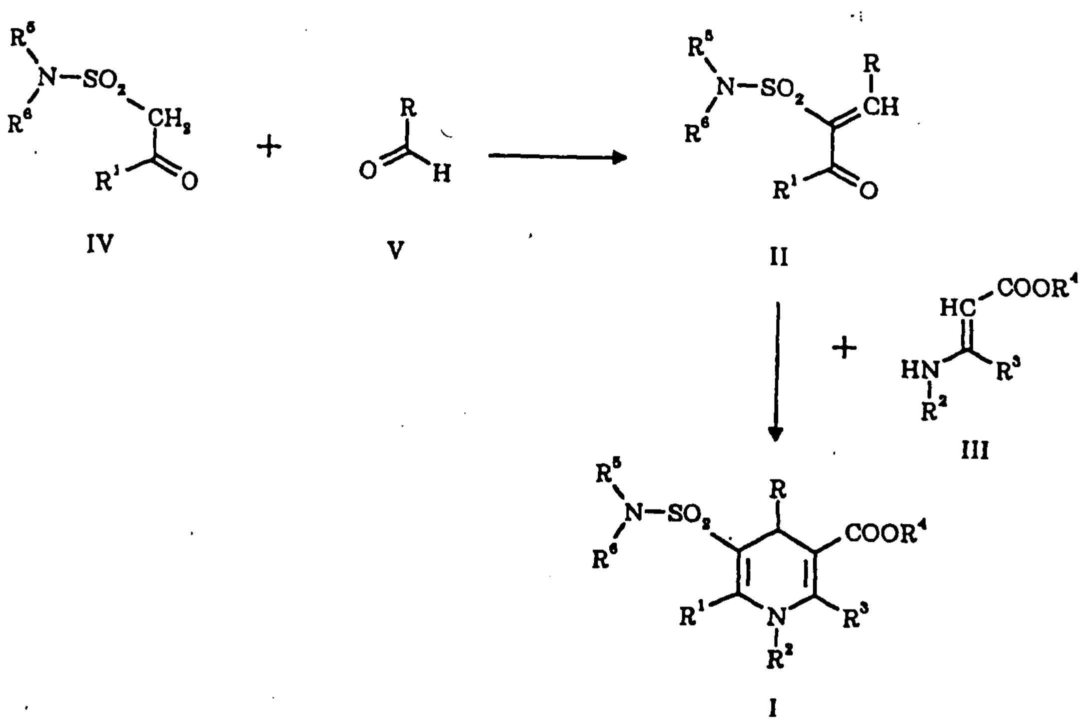




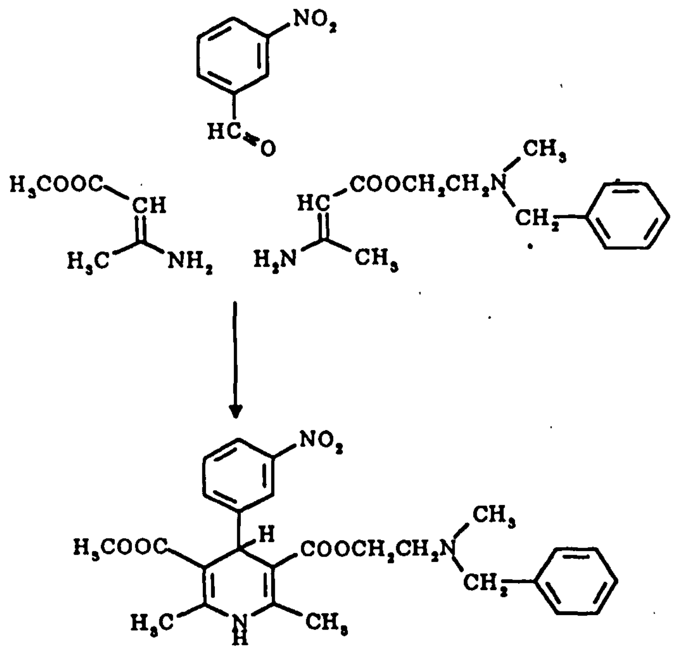
EP - 0371492 discloses that when the latter reaction (R"=2-haloethyl) is carried out in the presence of a dehydrating agent such as molecular sieves, the desired aryldihydropyridine product is obtained in improved yields and with fewer by-products.

Other analogous processes for the preparation of felodipine are known in the art (see for example: Span. Appl. Nos. ES-536,229; 537,424; and 549,753).

EP-0 212 107 describes the preparation of 5-sulfamoyl substituted 1,4-dihydropyridine derivatives according to the following general synthesis:

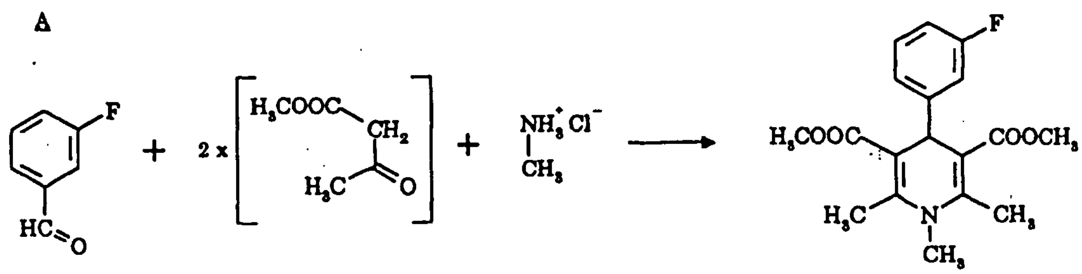


EP-0 445 987 describes the preparation of 1,4-dihydropyridines, for example nicardipine, according to the following general synthesis:

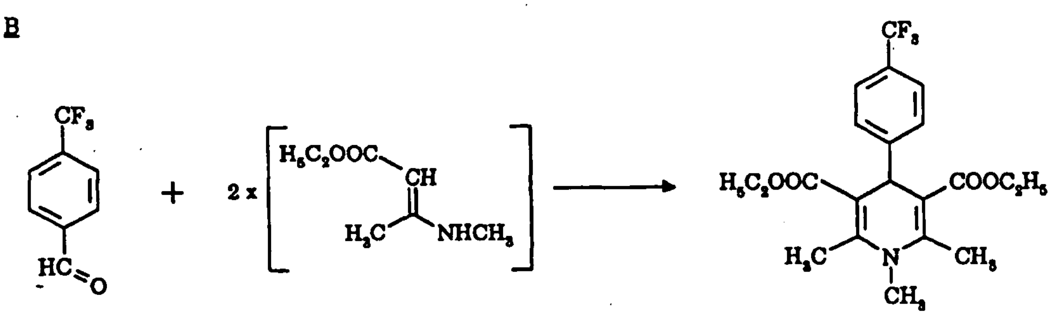


EP-0 451 654 describes the preparation of N-alkylated 1,4-dihydropyridine 3,5-diesters acccording to the following general syntheses:

A



B



An overview of dihydropyridine chemistry is provided by "Industrial & Engineering Chemistry, Product Research and Development", (1982), 21(2), pages 139-261.

In most of the disclosed syntheses of aryldihydropyridine diesters isolation of the product from the reaction mixture required an extractive workup that typically employed a halogenated solvent. Also because a low-molecular-weight alcohol is typically employed as a solvent in the cycloaddition reaction, such an extractive workup of the crude reaction requires that the solvent first be distilled away.

It is an object of the instant invention to provide a process, for the preparation of 4-substituted-1,4-dihydropyridines having shorter thermal reaction times, and, as a consequence, having lower weight percentages of undesirable impu-

rities, than processes previously known in the art.

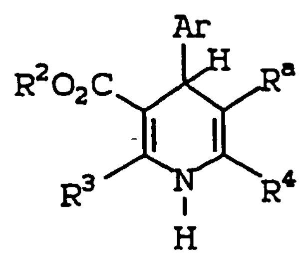
It has been surprisingly discovered that, under optimal reaction conditions designed to minimize the formation of impurities, the ring closure in the cycloaddition reaction of substituted 3-aminocrotonate and substituted benzylidene is not thermally driven to completion; rather, a strong acid can be added to the reaction mixture subsequent to the foreshortened heating period to catalyze and facilitate the complete cyclization to provide the 4-substituted-1,4-dihydropyridine.

It is also an object of the instant invention to provide an improved process for the preparation of felodipine having higher yields than processes previously known in the art.

It is further an object of the instant invention to provide a process for the preparation of felodipine wherein the crude felodipine is isolated by filtration of the reaction mixture, thereby eliminating the need for a more expensive and time-consuming extractive isolation procedure, which might employ environmentally harmful halogenated solvents.

SUMMARY OF INVENTION

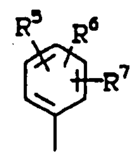
The present invention provides a novel process for the preparation of a compound having the formula I:

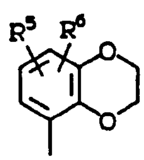


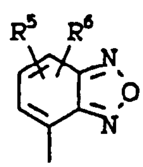
I

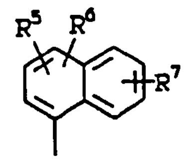
wherein

Ar is selected from:

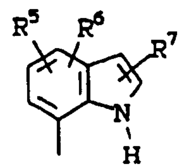
a)  ,

b)  ,

c)  ,

d) ,

and

e) ;

R^a is selected from:

a) $\overset{O}{\overset{\|}{C}}OR^1$,

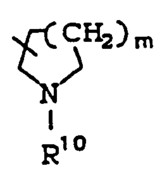
b) $\overset{X}{\overset{\|}{C}}NR^8R^9$,

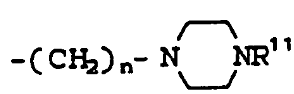
and

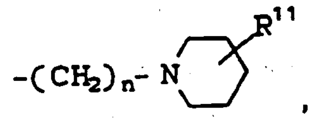
c) CN;

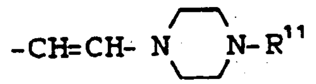
R^1 and R^2 are independently selected from:

a) C_1-C_8-alkyl,
b) C_3-C_8-cycloalkyl,
c) C_2-C_5-alkenyl,
d) C_1-C_4-aralkyl,
e) C_2-C_4-aralkenyl
f) -C_1-C_5-alkylNR^8R^9,
g) -C_1-C_4-alkyl-O-C_1-C_4-alkyl,
h) -C_1-C_4-alkylONO_2,

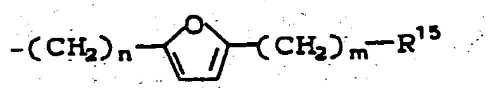
i) ,

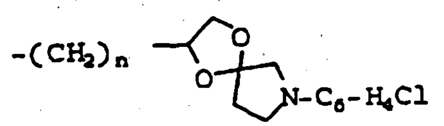
j) ,

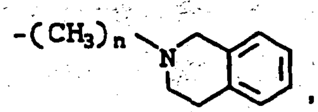
k) 

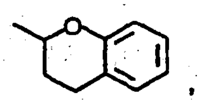
l) 

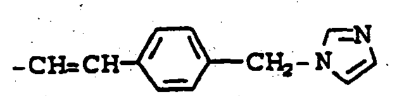
m) $-(CH_2)_n-\overset{O}{\overset{\|}{C}}-CH_3$,

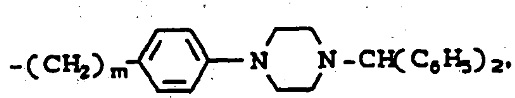
n) 

o) 

p) 

q) 

r) 

s) 

and
t) $-(CH_2)_mC_3$-C_8-cycloalkyl;

wherein C_1-C_4 aralkyl is selected from C_1-C_4 alkyl subustituted one to two times with a group selected from: phenyl and naphthyl;
wherein C_2-C_4 aralkenyl is selected from C_2-C_4-alkenyl substituted one to two times with a group selected from: phenyl and naphthyl;

R^3 is selected from:

a) C_1-C_8-alkyl,
b) C_3-C_8-cycloalkyl,
c) $(CH_2)_n$-R^{12}, and
d) hydrogen;

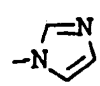
R^4 is selected from:

a) C_1-C_8-alkyl,
b) C_3-C_8-cycloalkyl,
c) $(CH_2)_n$-R^{12} and
d) hydrogen;

R^5, R^6, and R^7 are independently selected from:

a) hydrogen,
b) halogen,
c) NO_2,
d)
e) CF_3,
f) C_1-C_8-alkyl,
g) C_3-C_8-cycloalkyl,
h) ethynyl,
i) $-(CH_2)_n$-R^{12},

j)


,

and
k) $-O-(CH_2)_n-NH-CH_2-CH(OH)CH_2-O(C_6H_5)$;

R^8 and R^9 are independently selected from:

a) C_1-C_8-alkyl,
b) C_3-C_8-cycloalkyl,
c) C_1-C_4-aralkyl as defined herein above, and
d) hydrogen;

R^{10} is selected from:

a) hydrogen,
b) C_1-C_8-alkyl,
c) C_3-C_8-cycloalkyl, and
d) C_1-C_4-aralkyl;

R^{11} is selected from:

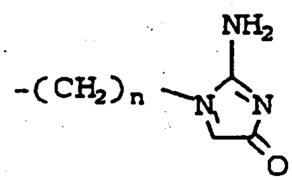
a) hydrogen,
b) C_1-C_4-aralkyl,
c) dichlorophenyl,
d) C_1-C_8-alkyl, and
e) C_3-C_8-cycloalkyl;

R^{12} is selected from:

a) halogen,
b) NR^8R^9,
c) $NHC(O)$-C_1-C_8-alkyl;
d) SR^8,
e) SO_2-pyridyl,
f) OR^8, and
g) CO_2R^8;

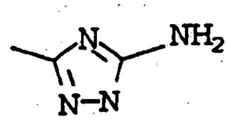
R^{13} is selected from:

a) $(CH_2)_n$-NHR^{14},
b) $-C(O)NH_2$,
c) $-(CH_2)_n$-$NHCH_2C(O)NH_2$, and

d)  ;

R^{14} is selected from:

a) hydrogen and

b)  ;

R^{15} is selected from:

a) $-NR^8R^9$, and
b) -1-piperdinyl;

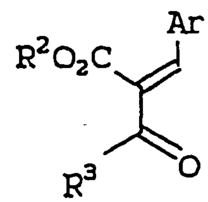
X is O, S or NR^8;

m is 0 to 2; and

n is 0 to 3;

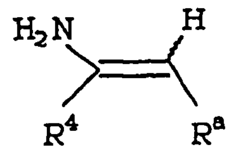
comprising the steps of:

a) heating a mixture of a benzylidene of the formula II:



II

wherein Ar, R^2, and R^3 are as defined hereinabove and a compound of the formula III:



III

wherein R^a and R^4 are as defined hereinabove, in a solvent at an elevated temperature and for a length of time between 5 minutes and 10 hours; and

b) then adding a strong acid to the reaction mixture;
to form the compound of the formula I.

The term "C_1-C_8-alkyl" includes straight and branched chain alkyl groups having from 1 to 8 carbons. The term C_1-C_8-alkyl includes methyl, ethyl, isopropyl, propyl, butyl, sec-butyl, t-butyl, and n-pentyl.

The term "C_3-C_8-cycloalkyl" includes cyclic alkyl groups having from 3 to 8 carbons. The term C_3-C_8-cycloalkyl includes cyclopropyl, and cyclobutyl.

The term "C_2-C_5-alkenyl" includes straight and branched chain carbons groups having from 2 to 5 carbon atoms and having one unsaturated bond. The term-includes vinyl, allyl, and 2-butenyl.

The term "solvent" includes water miscible solvents and water immiscible solvents. The preferred solvent is a water miscible solvent.

The term "water miscible solvents" include low-molecular-weight alcohols, acetonitrile, dimethylformamide (DMF), tetrahydrofuran (THF), dioxane, methoxyethanol, tetramethylene sulfone,and dimethoxyethane. The preferred water miscible solvent is a low-molecular-weight alcohol.

The term "water immiscible solvent" includes benzene, toluene, xylenes, chlorobenzene, o-dichlorobenzene, chloroform, methylene chloride, 2,2,4-trimethylpentane, and Dowtherm™.

The term "low-molecular-weight alcohol" includes hydroxy alkane compounds having from 1 to 4 carbon atoms and includes branched and straight chain and cyclic alcohols. The term includes methanol, ethanol, iso-propanol, butanol, isobutanol, and cyclohexanol.

The term "halogen" includes chlorine, fluorine, bromine, and iodine.

The term "elevated temperature" represents an temperature sufficiently high to maintain conversion of the starting materials but also sufficiently low to avoid decomposition of the starting materials, intermediates and the product of the formula I. The term includes temperatures between 35°C and 285°C. A preferred temperature is between 65°C and 130°C.

The term "length of time" represents a period of time sufficiently long to consume the maximum amount of the starting materials but sufficiently short to allow only a minimum amount of the starting materials, intermediates or product to decompose. The term includes times of 5 minutes to 10 hours. A preferred length of time is a time length between 30 mins and 2 hours.

The term "strong acid" includes aqueous acid solutions, non-aqueous acid solutions and gaseous acids.

The term "aqueous acid solution" includes aqueous mineral acids, optionally with a low-molecular-weight alcohol

co-solvent.

The term "non-aqueous acid solution" includes solutions of acids in a water miscible solvent, concentrated sulfuric acid, methane sulfonic acid, trifluoromethane sulfonic acid, nitric acid, dhloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid or amberlite™ sulfonic acid resin . The term also includes solutions of Lewis acids, such as aluminum chloride, and-the hydrolytic products of addition of a Lewis acid to a aqueous or protic medium.

The term gaseous acids include hydrogen chloride gas, hydrogen bromide gas, and hydrogen fluoride gas.

The term "aqueous mineral acid" includes aqueous hydrogen chloride, aqueous hydrogen bromide, aqueous hydrogen iodide, aqueous phosphoric acid, and aqueous perchloric acid. Apreferred aqueous mineral acid is aqueous hydrogen chloride.

It is understood that if any functional group substituent, which is part of the starting materials or product of the process disclosed in the instant invention, is incompatible with the chemical transformations of the instant invention (i. e., a particular carboxylic ester may be particularly labile in an acidic solution) a person of ordinary skill in the art would not choose a starting material containing such a group. Alternatively, the incompatible group may be selectively protected, by techniques known in the art, prior to employing a starting material in the process of the instant invention; and subsequent to isolation of such a "protected" product of the instant process, the protection may be removed from the substituent by techniques well known in the art.

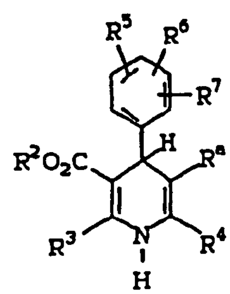
It is intended that the definition of any substituent (e.g., R^8, R^9, R^{12}, etc.), which may occur more than once in a particular compound, is independent of its separate occurances. Thus, in a given compound, R^3 may be $-CH_2R^{12}$ where R^{12} is OCH_3 and R^4 may be $-CH_2R^{12}$ where R^{12} is chlorine.

In a class of this embodiment of the process of the instant invention is that process wherein the low-molecular-weight alcohol is ethanol or isopropanol.

In a subclass of this embodiment is the process wherein the solution of aqueous hydrochloric acid in a low-molecular-weight alcohol is 6N aqueous HCl in ethanol.

In another class of this embodiment of the instant invention is the process wherein the internal reaction temperature is 84°C.

In another embodiment of the present invention is the process for the preparation of a compound having the formula Ia:



Ia

wherein

R^a is selected from:

a) $\overset{O}{\overset{\|}{C}}OR^1$,

b) $\overset{O}{\overset{\|}{C}}NR^8R^9$,

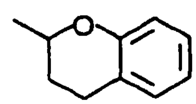
and
c) CN;

R^1 and R^2 are independently selected from:

a) C_1-C_8-alkyl,
b) C_3-C_8-cycloalkyl,
c) C_2-C_6-alkenyl,
d) C_1-C_4-aralkyl,
e) C_2-C_4-aralkenyl,
f) -C_1-C_4-alkyl-O-C_1-C_4-alkyl,
g) -C_1-C_4-alkyl-ONO_2,

h) $-(CH_2)_n-\overset{O}{\overset{\|}{C}}\ CH_3$,

and

i)  ;

R^3 is selected from:

a) CH_3,
b) CH_2F,
c) CN, and
d) CH_2-SO_2-pyridyl;

R^4 is selected from:

a) CR_3,
b) (CH_2)-NR^8R^9, and
c) $(CH_2)n$-OR^{12};

R^5, R^6, and R^7 are independently selected from:

a) hydrogen,
b) halogen,
c) NO_2,

d) $-CH{=}CH-O-\overset{O}{\overset{\|}{C}}-t\text{-}Bu$,

e) C_1-C_8-alkyl, and
f) -O-$(CH_2)_n$-NH-$CH_2CH(OH)CH_2O(C_6H_5)$;

R^8 and R^9 are independently selected from:

a) C_1-C_8-alkyl,
b) C_3-C_8-cycloalkyl,
c) C_1-C_4-aralkyl, and

d) hydrogen;

R^{10} is selected from:

a) hydrogen,
b) methyl, and
c) C_1-C_4-aralkyl;

R^{11} is selected from:

a) hydrogen,
b) C_1-C_4-aralkyl, and
c) dichlorophenyl;

R^{13} is selected from:

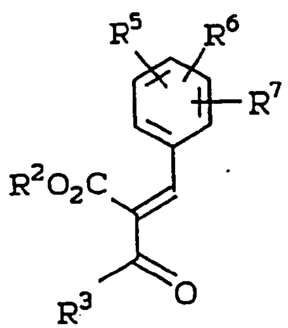
a) $-C(O)NH_2$, and
b) $(CH_2)_n$-$NHCH_2C(O)NH_2$;

R^{14} is hydrogen;

m is 0 to 2; and

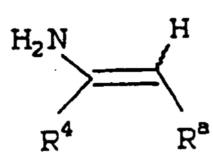
n is 0 to 3;

comprising the steps of:
heating a mixture of a benzylidene of the formula IIa:



IIa

wherein R^2, R^3, R^5, R^6 and R^7 are as defined hereinabove and a compound of the formula III:

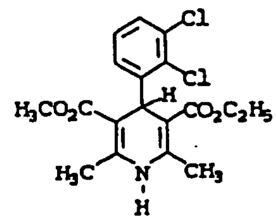


III

wherein R^a and R^4 are as defined hereinabove, in a solvent which is a water miscible solvent at an elevated temperature and for a length of time between 5 minutes and 10 hours;

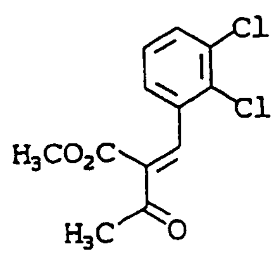
THEN TREATING the reaction mixture with an aqueous acid solution to provide the compound of the formula Ia.

A class of this embodiment of the present invention is the process for the preparation of felodipine, having the formula Ib:



Ib

COMPRISING THE STEPS of heating a mixture of a dichlorobenzylidene of the formula IIb:



IIb

and ethyl 3-aminocrotonate in a low-molecular-weight alcohol at an elevated temperature and for a length of time between 30 minutes and 6 hours; and
ADDING a strong acid to the reaction mixture;
to provide felodipine.

A subclass of this class of the present invention is the process which further comprises the steps of:
COOLING the solution to cause crystallization, AND collecting the crude felodipine by filtration.

In a subclass of this class of the instant invention is the process wherein the strong acid is a 1:1 v/v mixture of 6N aqueous HCl and ethanol.

In another subclass of this class of the instant invention is the process wherein the strong acid is selected from a 1:1 v/v mixture of 6N aqueous HCl and isopropanol; concentrated (37%) aqueous HCl or anhydrous methane sulfonic acid.

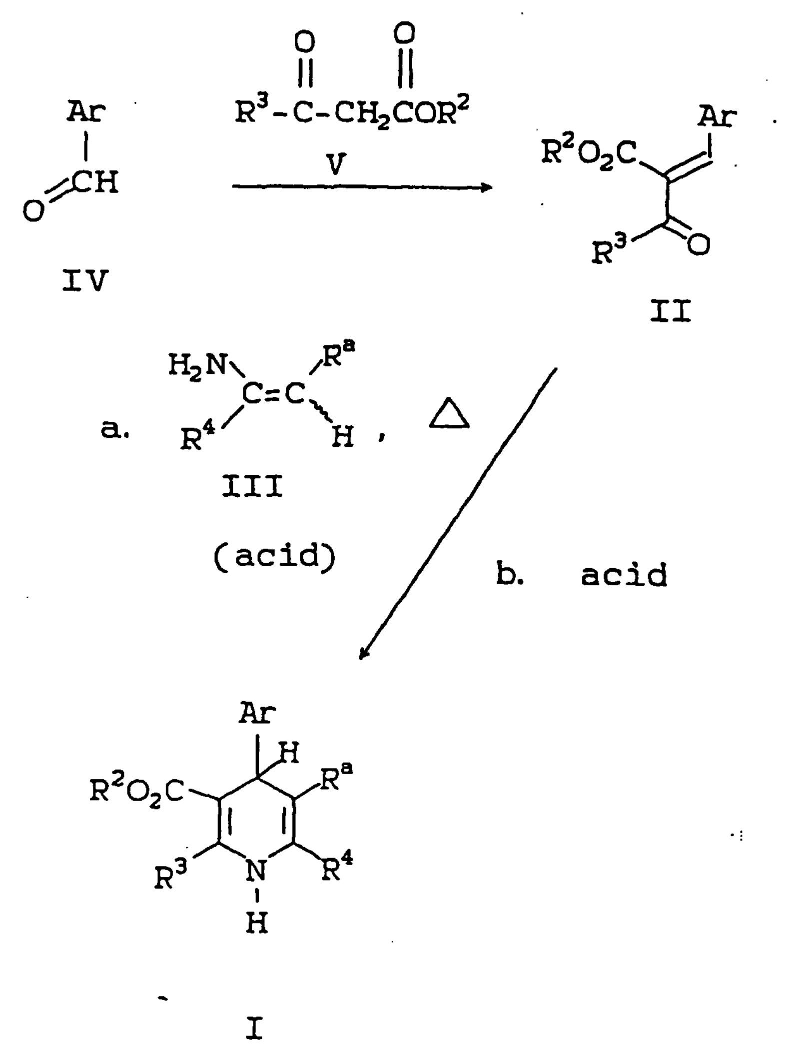
In another subclass of this class of the instant invention is the process which further comprises the step of heating the reaction mixture containing the strong acid for an additional length of time at an elevated temperature.

In another subclass of this class of the instant invention is the process wherein ethyl 3-aminocrotonate is used in molar excess to the dichlorobenzylidene of the formula IIb and the molar amount of strong acid added to the reaction mixture is equal to approximately the molar excess of ethyl 3-aminocrotonate employed.

DETAILED DESCRIPTION OF THE INVENTION

The following synthetic Scheme 1 illustrates a reaction sequence in which the process of the instant invention is employed.
The substituents Ar, R^a, R^2, R^3, and R^4 are as defined hereinabove.

Scheme 1



The starting compounds (compounds III, IV and V) employed in the synthetic scheme are known in the art and are readily available either commercially or by following the procedures described in the literature. For example, syntheses of such starting compounds are described in the following patents and publications: U.S. Pat. Nos. 4,220,649; 4,264,611; 4,705,797; 4,769,374; 4,772,596, 4,806,544; 4,874,773; EPO Application Nos. O 089 167, O 095 451, O 063 365, O 257 616, O 319 814, O 342 182, 0 370 821, 0 370 974, 0 371 492, and S.M. Jain et al., Indian J. Chem., 29B, 95 (1990).

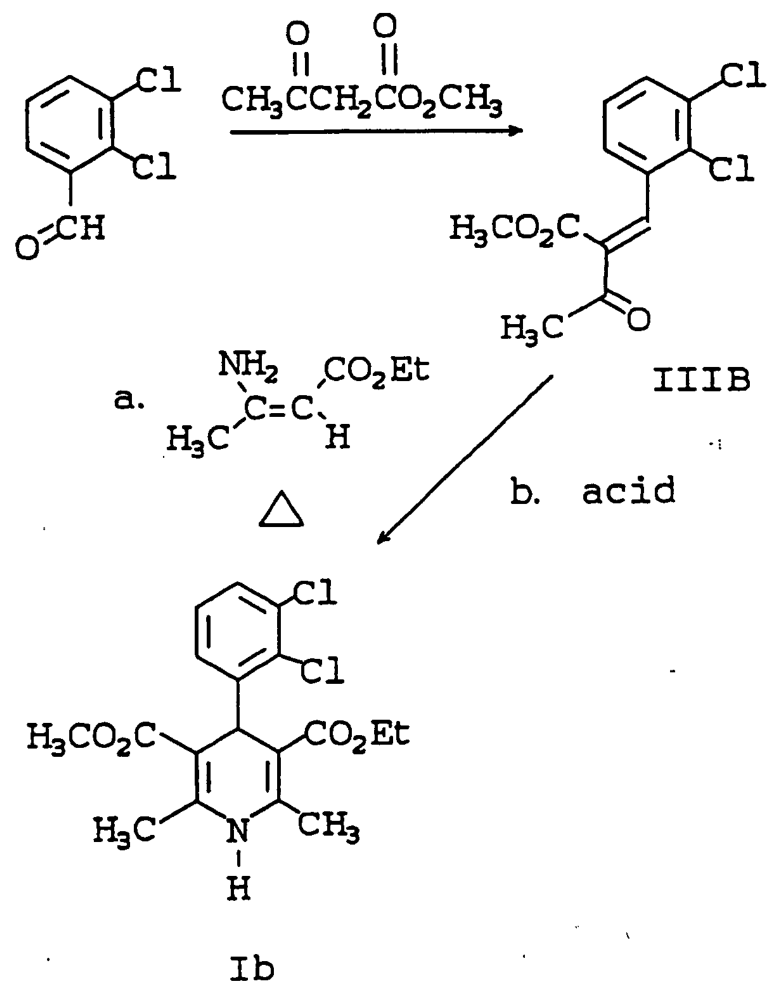
In words relative to the equations, the suitably substituted benzaldehyde, VI, such as 3-nitrobenzaldehyde, 2-nitrobenzaldehyde, and 2,3-dichlorobenzaldehyde, is reacted with a suitably substituted β-keto acid ester V, such as ethyl acetoacetate, methyl acetoacetate, and cyclopropyl acetoacetate, in the presence of a suitable catalyst, such as acetic acid, piperidine, a mixture of acetic acid and piperdine,to provide the benzylidine II. The benzylidene II is reacted with a suitably substituted enamine III, such as ethyl 3-aminocrotonate, and 3-aminocrotonic proparygylamide, in a suitable low-molecular-weight alcohol solvent, such as methanol, ethanol, and isopropanol, and the mixture was heated at reflux for 10 minutes to 10 hours. The molar ratios of compound II to compound III employed in the the reaction is in the range between 0.66 and 1,5. Preferably, heating is continued until the limiting reagent (whichever of compound II and compound III is not in excess) is consumed. The heating source present in the reaction mixture, the heating source may be removed, and the mixture may be cooled slightly, and a strong acid, such as aqueous hydrogen chloride solution, aqueous sulfuric acid solution, and anhydrous methane sulfonic acid, which may contain additional co-solvents, such as water, ethanol, isopropanol, and dimethoxyethane or mixtures thereof, is added slowly. The reaction

product may then be recovered by extractive workup with a suitable organic solvent, such as methylene chloride, and ethyl acetate, or may be isolated, where possible, by cooling and, optionally seeding, the crude reaction mixture, thereby inducing crystallization of the neutral compound or its acid salt when that species is formed, and by subsequently collecting the product by filtration.

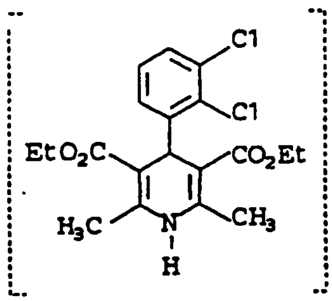
Alternatively, a strong acid as described above may be added after the initial heating period and the reaction may be heated for an additional time, such as a period selected from 10 minutes to 2 hours. The reaction mixture may then be cooled and the reaction product may be recovered as described above by extractive workup or by cooling/seeding/ filtration.

The following Scheme 2 illustrates a reaction sequence in which the process of the instant invention is employed in the synthesis of felodipine.

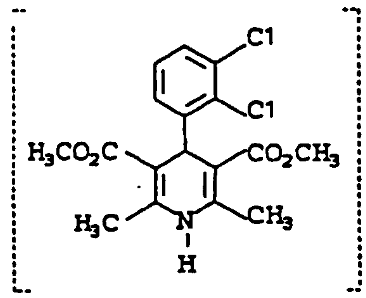
Scheme 2



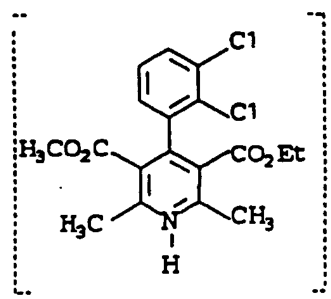
Scheme 2 (continued)



Ic



Id



Ie

The reagents employed in the synthetic scheme are well known in the art and are all readily commercially available.

In words relative to the equations, 2,3 - dichlorobenzaldehyde is reacted with methyl acetoacetate, in the presence of a suitable catalyst, such as piperidine, acetic acid, and a mixture ofpiperidine and acetic acid, to provide after aqueous workup the dichlorobenzylidene IIa. A mixture of the benzylidene IIa and ethyl 3-aminocrotonate in a suitable low-molecular-weight alcohol solvent, such as methanol, ethanol, and isopropanol, is heated at reflux for a suitable period of time, such as a time between 30 minutes and 20 hours. The concentration of the reactants in the solvent may be selected from a range of 0.5 mmoles of the dichlorobenzylidene IIa/mL of solvent to 5 mmoles of IIa/mL of solvent. Preferred is a concentration of 1.0 mmole of IIa/mL of solvent. The mixture may then be cooled slightly and a solution of aqueous HCl and a suitable low-molecular-weight solvent, such as 6N aqueous HCl and ethanol is added dropwise to the mixture. The mixture is then further cooled, the product thereby crystallizing out of solution and the product was then collected by filtration, rinsed with appropriate solvents, such as cold aqueous ethanol solutions, and dried under vacuum. The crude product may contain small quantities of compounds of Formulas Ic, Id and Ie as minor impurities. The crude product Ia thus obtained can subsequently be recrystallized from an appropriate solvent, such as an isopropanol/water mixture.

Alternatively, a strong acid as described above may be added after the initial heating period and the reaction may be heated for an additional time, such as a period selected from 10 minutes to 2 hours. The reaction mixture may then be cooled and the reaction product may be recovered as described above by extractive workup or by cooling/seeding/filtration. A particular method of direct isolation by crystallization and filtration comprises the addition of water or another solvent such as methyl-t-butylether to the reaction mixture after the additional heating period.

The invention is further defined by reference to the following examples. For instance, it is understood that the following known vasodialators/calcium channel blockers may be prepared by reactions similar to the reactions set out in the examples: amlopine, cronidipine, diperdipine, furaldipine, lacidipine, manidipine, mepirodipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, sagandipine and taludipine.

In the Examples all temperatures are in degrees Celsius. All purity percentages disclosed were determined by HPLC (reverse phase C-18 column; MeOH/CH_3CN/phosphate at pH3 elution; detector at 254nm) and yields given are based on pure felodipine. Pot temperatures represent actual temperature of the reaction solution as determined by an in situ digital thermometer.